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EXAMINER
DIBRINO, MARIANNE NMN

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/669,925

Applicant(s)

HILDEBRAND ET AL.

Examiner

DiBrino Marianne

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-42, 45-51, 60 and 61 is/are pending in the application.
- 4a) Of the above claim(s) 38-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-37, 42, 45-51, 60, 61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

1. Applicant's amendment and response filed 8/20/07 is acknowledged and has been entered.
2. Applicant is reminded of Applicant's election of Group I (claims 1-21, 30-51, 62-82 and 92), and species of ELISA plate as the substrate, antibody as the anchoring moiety, W6/32 as the antibody, as well as Applicant's election of the species of HLA-A2 with traverse in Applicant's amendment and response filed 12/1/06.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include the species of magnetic bead and nylon membrane recited in instant 37.

Claims 31-37, 42, 45-51, 60 and 61 are currently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 8/20/07.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 31-37, 42, 45-51, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the disclosure as originally filed is as follows:

a. "providing a pool of...MHC trimolecular complexes, each trimolecular complex comprising a recombinant, soluble MHC heavy chain allele..." recited in base claim 31 and "pool of functionally active... soluble MHC trimolecular complexes" in instant claim 42. Although the said base claim later recites that the MHC trimolecular complexes are produced by a method comprising identifying and amplifying an MHC heavy chain allele, "comprising" encompasses other method steps and other identified and amplified MHC heavy chains that are not the same allele product; therefore, the pool of MHC trimolecular complexes may comprise more than one MHC allele product, *i.e.*, not the same soluble MHC heavy chain allele product. Applicant does not point to support in the disclosure for the claim amendment.

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b. "at least one MHC trimolecular complex linked thereto" recited in instant base claim 31, "at least one MHC trimolecular complex" recited in claim 35 and in claim 61. Applicant does not point to support in the disclosure for the claim amendments.

5. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed a method for detecting the presence of anti-HLA antibodies in a sample wherein the solid support used in the method is a combination of solid supports such as those recited in the instant claims. The instant claim encompasses a solid substrate that is more than one type or component of solid substrate.

=The specification discloses at ([0120]) "The assay of the presently claimed invention is performed by first attaching sHLA molecules to a substrate, such as a solid support. The substrate may be any insoluble support to which the sHLA molecule can be bound, either directly or indirectly, which is readily separable from soluble material, and which is otherwise compatible with the overall methods of the present invention. The surface of such substrates may be solid or porous, and the substrates may have any shape that allows the substrate to function in accordance with the present invention. Examples of substrates that may be utilized in accordance with the present invention include, but are not limited to, microtiter plates, such as but not limited to ELISA plates; membranes, such as but not limited to, nitrocellulose membranes, PVDF membranes, nylon membranes, acetate derivatives, and combinations thereof; fiber matrix, SEPHAROSE matrix, sugar matrix; plastic chips; glass chips; or any type of bead, such as but not limited to, LUMINEX beads, DYNABEADS, magnetic beads, flow-cytometry beads, and combinations thereof. The substrates are typically formed of glass, plastic or any other type of polymer, such as but not limited to PVC, polyvinyl propylene, polyethylene and the like, polysaccharides, nylon, nitrocellulose, and combinations thereof. Microtiter plates are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples. Where separations are made by magnetism, the support generally includes paramagnetic components, preferably surrounded by plastic."

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The specification discloses no working examples or description with regards to making or using solid substrates that are combinations or composites of the substrates recited in the instant claims.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

6. Claims 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a method for detecting the presence of anti-HLA antibodies in a sample wherein the solid support used in the method is a combination of solid supports such as those recited in the instant claims. The specification has not enabled the breadth of the claimed invention because the claims encompass use of a solid substrate that is more than one type or component of solid substrate. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be made practiced.

The specification discloses at ([0120]) "The assay of the presently claimed invention is performed by first attaching sHLA molecules to a substrate, such as a solid support. The substrate may be any insoluble support to which the sHLA molecule can be bound, either directly or indirectly, which is readily separable from soluble material, and which is otherwise compatible with the overall methods of the present invention. The surface of such substrates may be solid or porous, and the substrates may have any shape that allows the substrate to function in accordance with the present invention. Examples of substrates that may be utilized in accordance with the present invention include, but are not limited to, microtiter plates, such as but not limited to ELISA plates; membranes, such as but not limited to, nitrocellulose membranes, PVDF membranes, nylon membranes, acetate derivatives, and combinations thereof; fiber matrix, SEPHAROSE matrix, sugar matrix; plastic chips; glass chips; or any type of bead, such as but not limited to, LUMINEX beads, DYNABEADS, magnetic beads, flow-cytometry beads, and combinations thereof. The substrates are typically formed of glass, plastic or any other type of polymer, such as but not limited to PVC, polyvinyl propylene, polyethylene and the like, polysaccharides, nylon, nitrocellulose, and combinations thereof. Microtiter plates are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples. Where separations are made by magnetism, the support generally includes paramagnetic components, preferably surrounded by plastic."

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The specification discloses no working examples with regards to making or using solid substrates that are combinations or composites of the substrates recited in the instant claims.

Evidentiary reference Zaer *et al* (Transplantation. 1997, 63(1): 48-51, IDS reference) teach that ELISA plates are used alone as a solid support to adsorb HLA complexes to the said support in order to screen for anti-HLA antibodies in patient sera (especially last paragraph at column 2 on page 48).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 50 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 is indefinite in the recitation of "MHC trimolecular complexes purified by..." because it is not clear what is meant, *i.e.*, if "MHC trimolecular complexes are purified by..." is what is meant.

9. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.*, 9/24/03, as the parent applications do not support the claimed limitations of the instant application. The provisional parent application serial no. 60/413,842 only discloses ELISA assays using W6/32 or pan-HLA antibody immobilized HLA to detect anti-HLA antibodies. The provision parent application serial no. 60/474,655 discloses some aspects of making soluble HLA from gDNA or cDNA. The parent application serial no. 10/337,161 and 10/022,066 disclose soluble HLA and making soluble HLA, respectively. In addition, the provisional parent applications do not disclose "pool" and "at least one MHC trimolecular complex" as enunciated at item #4 *supra* of this Office Action.

Applicant's arguments in the amendment filed 8/20/07 have been fully considered, but are not persuasive.

Applicant's arguments are of record in the said amendment on page 36, briefly that "the parent applications are more than amply disclose the presently claimed invention."

It is the Examiner's position that Applicant's argument is not persuasive for the reasons enunciated *supra*.

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10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 31-37, 42, 45-51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of U.S. Patent No. 5,292,641 (IDS reference), Prilliman *et al* (Immunogenetics. 1997, 45: 379-385, IDS reference), DiBrino *et al* (Biochemistry. 1995, 34(32): 10130-10138, of record) and U.S. Patent No. 6,232,445 B1 (IDS reference).

U.S. Patent No. 5,482, 841 discloses an assay method for detecting the presence of anti-HLA antibodies in a sample, said assay comprising HLA molecules extracted from cells and purified by detergent extraction, centrifugation, PEG and NH_4SO_4 precipitation, said HLA molecules indirectly linked to a solid support such as beads, membranes and microtiter plates by polyclonal or monoclonal antibodies specific for the $\alpha 3$ domain of Class I HLA or the associated $\beta 2\text{m}$ chain or to a conformational epitope expressed by the combination of both chains, or specific to epitopes conserved across a class or subset of HLA molecules, such as ones specific for HLA-A, B or C. U.S. Patent No. 5,482, 841 further discloses that a sample containing antibodies is added, bound antibodies are separated from free antibodies and other non-specifically bound proteins or other components, and the presence of the antibodies is detected using a labeled reagent such as anti-human antibody against IgG, IgM or IgA. U.S. Patent No. 5,482, 841 discloses that the samples may be biological fluids such as blood, CSF, tears, saliva, lymph, dialysis fluid, organ or tissue culture derived fluids and fluids extracted from physiological tissues. U.S. Patent No. 5,482, 841 discloses that of particular interest are allo-antibodies found in the serum of transplant or prospective transplant patients, and that the determination of the presence and specificity of antibodies against foreign HLA antigens is therefore clinically important for monitoring transplant patients, and the assay may test for reactivity against a panel of antigens or may be specific for a single donor. U.S. Patent No. 5,482, 841 discloses that the solid support can be microtiter plates (with wells), glass, plastic, polysaccharides, nylon or nitrocellulose or paramagnetic component materials surrounded by plastic. U.S. Patent No. 5,482, 841 discloses using negative and positive control samples. U.S. Patent No. 5,482, 841 discloses a kit for use in a method for detecting at least one receptor analyte specific for an HLA antigen in a biological sample, said kit comprising a solid support coated with a capture agent capable of specifically binding to a conserved region of a subset of interest of HLA antigens and a labeled reagent that specifically binds to human antibodies, and wherein the capture agent may be an antibody directed to the $\alpha 3$ domain of HLA class I heavy chain (see entire reference).

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U.S. Patent No. 5,482, 841 does not disclose wherein the pool of HLA molecules is recombinantly produced.

U.S. Patent No. 5,292,641 discloses a kit that includes HLA antigens bound to a solid support, control solutions, and the reagents necessary for the determination of antibodies specific for the HLA antigens (especially column 5 at lines 35-49). U.S. Patent No. 5,292,641 discloses an assay method that utilizes HLA bound to a solid support, said HLA being Class I or Class II or minor histocompatibility antigens and derived from human donors, including from platelets, plasma, serum, lymphoblastoid cell lines, transfectant cell lines, or any other convenient source, said solid support including microtiter plate wells, test tubes, beads, slides, absorbent films, membranes, particles, magnetic particles, glass or plastics. U.S. Patent No. 5,292,641 discloses ELISA techniques and the use of labeled anti-human bodies for detection (see entire reference).

Prilliman *et al* teach large-scale production of Class I HLA in roller bottles (*i.e.*, recombinantly produced in a large scale mammalian tissue culture system) for expansion of transfected cells for inoculation into a CELL-PHARM hollow fiber bioreactor for high yield production of Class I HLA. Prilliman *et al* further teach a full-length, single stranded cDNA clone of HLA-B*1501 was used as template in PCR amplification with primers, the 3' primer of which introduces a TGA stop codon, truncating the expressed form of the molecule through removal of the TM and cytoplasmic exons from the coding region. Prilliman *et al* teach the PCR product directionally subcloned into M13, and then subcloned into the mammalian pBJ1-neo expression vector comprising a promoter, and the resulting construct transfected into the class I-negative EBVU-transformed lymphoblastoid line 721.221. The said line was grown in a large-scale culture system and the CELL-PHARM bioreactor, the soluble HLA collected, centrifuged, and subjected to affinity purification processing and fractionation (especially materials and methods section).

DiBrino *et al* teach obtaining and amplifying full length cDNA for HLA-B*4403 by PCR amplification of cDNA made from RNA isolated from the immortalized human lymphoblastoid B cell line W1B. The cDNA was sequenced, cloned into the expression vector RSV.neo and transfected into Hmy2.C1R cells (class I deficient cell line). DiBrino *et al* teach detection of said HLA using W6/32 monoclonal antibody specific for human Class I molecules. DiBrino *et al* teach HLA-A2 class I HLA molecules (especially materials and methods section).

U.S. Patent No. 6,232,445 B1 discloses that DNA encoding HLA, including HLA class I or class II, may be inserted into a vector with a promoter for expression in eukaryotic cells. U.S. Patent No. 6,232,445 B1 discloses that a variety of standard methods can be used to introduce a DNA segment encoding a desired MHC complex or DNA vector carrying the same into a desired cell, for example, by CaPO₄-mediated transfection or transformation, electroporation or liposome-mediated

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transfer. U.S. Patent No. 6,232,445 B1 discloses that cells are then cultured under conditions that support the expression of the MHC complex, such as hollow fiber culture systems, roller bottles, bioreactors or fermentors. U.S. Patent No. 6,232,445 B1 discloses that the cells may be mammalian cells (that produce occupied MHC molecules) or other eukaryotic cells such as insect cells, and in the latter instance, a variety of presenting peptides can be loaded or covalently linked to MHC complexes, and the MHC molecules may also be single-chain molecules. U.S. Patent No. 6,232,445 B1 discloses isolating total RNA from a human lymphocyte cell line that expresses an MHC class II gene, generating cDNA by PCR, and using oligonucleotide primers that truncate the extracellular portions of the class II molecule, inserting the truncated PCR product into a vector carrying a promoter, subcloning into an expression vector, including a mammalian expression vector, electroporating mammalian cells to transfect them with a plasmid vector, and selection and large scale production of the HLA molecule, as well as affinity chromatography and fractionation to purify the HLA molecules away from contaminating proteins, including use of antibodies that specifically recognize class I or class II MHC molecules (that produce "empty" MHC molecules) (especially column 28 at lines 28-67, columns 29-32, column 33 at lines 1-6 and Examples).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have provided recombinantly produced HLA molecules such as those taught by Prilliman *et al* and DiBrino *et al*, those HLA molecules produced recombinantly by the method steps taught by Prilliman *et al* and DiBrino *et al* and disclosed by U.S. Patent No. 6,232,445 B1, by isolating mRNA for said HLA molecule, reverse transcribing the mRNA to obtain cDNA, identifying an individual MHC heavy chain allele in the cDNA, amplifying cDNA by PCR using a primer that truncates after the extracellular region as per the teaching of DiBrino *et al* and as per the disclosure of U.S. Patent No. 6,232,445 B1, cloning the PCR product into a mammalian expression vector, electroporating the plasmid vector into a suitable host cell, and inoculating a CELL-PHARM or other hollow fiber bioreactor or large scale mammalian tissue culture system with said host cell(s), growing said host cells, and harvesting the soluble HLA molecules as per the teaching of Prilliman *et al* and as per the disclosure of U.S. Patent No. 6,232,445 B1, and purifying the HLA molecules as per the teaching of Prilliman *et al* and as disclosed by U.S. Patent No. 6,232,445 B1, including by use of the class I specific antibody W6/32 taught by DiBrino *et al* for production and use of class I HLA molecules, and including the use of W6/32 antibody as a capture agent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a source of HLA molecules for the method for detecting the presence of anti-HLA antibodies in a sample disclosed by the primary reference U.S. Patent No. 5,482, 841 since the secondary references Prilliman *et al*, DiBrino *et al*, and U.S. Patent No. 6,232,445 B1 teach or disclose methods of

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isolating, amplifying and large-scale production of specific HLA class I and class II allele products.

With regard to the inclusion of the instant claims in this rejection, although the art reference does not explicitly disclose that endogenous peptides are present in the binding groove of the extracted HLA molecules, the art reference does disclose that the HLA molecules are produced from mammalian cell lines; therefore, the HLA molecules would be expected to contain a mixture of endogenous peptides in their peptide binding grooves. Therefore, the claimed process appears to be the similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See *in re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments in the amendment filed 8/20/07 have been fully considered, but are not persuasive.

It is the Examiner's position that the limitations of canceled claim 44 have not been incorporated into instant base claim 31. Canceled claim 44 recites "wherein in the step of providing a substrate...the individual soluble HLA molecule is produced by a method comprising the steps of..." versus the recitation in claim 31 "the method comprising providing a substrate, providing a pool of functionally active, recombinantly produced, truncated individual soluble MHC trimolecular complexes...wherein the individual soluble MHC trimolecular complexes are produced by a method comprising...", i.e., the method recited in claim 44 contains a method step for producing the HLA molecules, whereas the method recited in claim 31 does not contain a method step for producing the HLA molecules but rather recites the method by which the HLA molecules that are provided were produced. It is the Examiner's further position that if such method step were included in base claim 31, the art method would meet the claim limitations.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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